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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,759	10/17/2003	Santosh R. D'Mello	119941-1100	1987

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GARDERE WYNNE SEWELL LLP
INTELLECTUAL PROPERTY SECTION
3000 THANKSGIVING TOWER
1601 ELM ST
DALLAS, TX 75201-4761

EXAMINER	
CRUZ, KATHRIEN ANN	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,759	D'MELLO ET AL.	
	Examiner	Art Unit	
	KATHRIEN CRUZ	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-11,13 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14,15,17-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-34 are pending.

Claims 1-11, 13 and 16 are withdrawn.

Claims 12, 15, 17-34 are examined herewith.

Applicants response filed October 30, 2008 has been received and entered into the application.

Priority

This application claims benefit to provisional application 60/419,439 (dated 10/18/2002) and provisional application 60/440,177 (dated 01/15/2003).

Action Summary

Claims 12, 14-15 and 17-19 and 22-27 rejection under 35 U.S.C. § 112, first paragraph is withdrawn. However, **claims 12, 20 and 21 rejection under 35 U.S.C. § 112, first paragraph is maintained.**

Response to Arguments

Applicant argues that the Examiner has not provided any evidence or reasoning to support the assertion that complete inhibition is unlikely with reasonable experimentation and it respectfully submitted that a prima facie case of nonenablement has not been established. MPEP 2164.04. This argument has been fully considered

but has not been found persuasive. Applicant has shown no data that demonstrates complete or at least partially inhibits neuronal cell death. The term "prevent" is interpreted to mean absolutely and completely stops or does not allow the beginning of neuronal cell death to occur in every instant and in every subject with **no exceptions**. And the term "at least partially" is interpreted to mean that the administration of GW5074 and ZM336372 will prevent the neuronal cell death. However, the Figures 10A-C show brain lesions in an in vivo experimental model of Huntington's disease. Applicant's assert that the figures demonstrate complete prevention of neurodegeneration. The figures seem only to indicate **a reduction** of the extensive bilateral striatal lesions induced by 3-NP with no data to quantify or qualify the data shown. Therefore, the rejection of claims 12, 20 and 21 rejection under 35 U.S.C. § 112, first paragraph is deemed proper and is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 28-34 are drawn to a method of

reducing neuronal cell death in a mammal, in which the specification does not reasonably provide support for such method, therefore this is new matter.

Claim 12, 14, 17-18, 20, 22-27 are rejected under 35 U.S.C.112, first paragraph, because the specification , while being enabling for making and using salts of the claimed compounds, does not reasonable provide enablement for making and using derivatives, complex, solvates or hydrates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni,* 195 USPQ 150, *ex parte formal*, 230 USPQ 546. a) Finding a solvates or hydrates is an empirical exercise. Predicting if a certain ester of claimed alcohol, for example, is in fact a solvates or hydrates, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo* , this is still an experimental science. For a compound to be a solvates or hydrates, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to

produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the solvates or hydrates is found in the specification on page 21. c) There is no working example of a solvates or hydrates of a compound the formula II. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrugs art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to fine a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicated the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the solvates or hydrates concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence is particularly relevant. f) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F2d 833, 839, 166 USPQ 18, 24 (CCPQ 1970). g) The breadth of the claims includes all of the hundreds of thousand of compounds

of formula of claim 12 as well as the presently unknown list of potential solvates or hydrates embraced by claim 12.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 14, 18-22, 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August 1999, 6:559-568).

Sweatt teaches that the amount of activated MAPK in a neuron can be reduced by approaches that cause dephosphorylation of upstream kinases in the MAPK cascade. Thus, compounds that activate phosphatases specific for any members of the MAPK cascade upstream of MAPK will reduce the activity of the upstream kinase, ultimately leading to reduced downstream activity of MAPK. Compounds that effect dephosphorylation of other upstream kinases including Ras, Raf1 (also known as c-raf), B-Raf and Rap1 may be used (paragraph 0027). Sweatt teaches that compounds

that inhibit the activity of kinases upstream of MAPK in the MAPK cascade include c-Rafs (paragraph 0032). Sweatt teaches that such compounds (e.g. c-Raf's) may be administered to humans and mammals (paragraph 0036). Sweatt teaches that c-raf may be used in the treatment of seizure disorders (abstract).

Sweatt does not expressly teach the c-Raf of N-[5-(3-Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide

Hall-Jackson teaches that N-[5-(3- Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide (herein after, "ZM 336372") is a potent and specific inhibitor of c-Raf that shows a tenfold selectivity over B-Raf (page 565, first paragraph under Discussion). Hall-Jackson teaches that cells (in mammals) have a feedback loop by which Raf suppresses its own activation, so that any inhibition of Raf is rapidly counterbalanced by its reactivation. This implies that cells does contain high specific activity c-Raf that is inhibited from activating its downstream substrate MKK1 because of the presence of the inhibitor (page 565, first paragraph under Discussion). Hall-Jackson teaches that ZM 336372 inhibits c-Raf and B-Raf (page 566, table 4 and first paragraph).

It would have been obvious to one of ordinary skills in the art at the time of the invention was made to employ the specific c-Raf, ZM 336372 to treat epilepsy (seizure disorder) or individuals susceptible to neurodegenerative disease. One would have been motivated to employ ZM 336372 because ZM 336372 is a potent and effective inhibitor of c-raf and B-raf as taught by Hall-Jackson.

Examiner further points out that any individual is susceptible to neurodegenerative disease as the individual ages and would benefit by the administration of c-Raf inhibitors.

With regards to the c-raf inhibitor (e.g. ZM 336372) inhibiting neuronal cell death via B-raf regulation, it is a property of the c-Raf that upon administration of a c-Raf to a mammal that inhibition of cell death via B-raf regulation would be obtained. Furthermore, presence of a property not possessed by the prior art is evidence of nonobviousness. *Inre Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of producing "regenerated cellulose consisting substantially entirely of skin'" whereas the prior art warned "this compound has practically no effect.' "). The submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979). See the discussion of latent properties and additional advantages in MPEP § 2145.

Claims 15, 17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August

1999, 6:559-568) as applied to claims 12, 14, 18-22, 24-27 above, and further in view of Varga (Involvement of Raf-1 in chronic ç-opioid receptor agonist-mediated adenylyl cyclase superactivation, European Journal of Pharmacology 451, 2002, 101-102).

Neither Sweatt nor Hall-Jackson expressly teach {5-iodo-3- [(3, 5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone} (herein after GW 5074).

Varga teaches that GW 5074 is a c-Raf inhibitor.

It would have been obvious to one of ordinary skills in the art to employ the specific c-Raf of GW 5074 for the treatment of individuals susceptible fo neurodegenerative diseases. One would be motivated to employ GW 5074 because GW 5074 is a c-Raf inhibitor as taught by Varga and everyone is susceptible for neurodegenerative disease and would benefit from the administration of GW 5074. Therefore, the claim limitations as set forth in claims 15, 17 and 23 have been met.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Claims 12, 14, 15, 17-34 are rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN CRUZ/
Examiner, Art Unit 1617

/San-ming Hui/
Primary Examiner, Art Unit 1617